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Professional continuous glucose monitoring in patients with diabetes mellitus: A systematic review and meta-analysis

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Abstract

Aim: To evaluate the effect on glucose control of professional continuous glucose monitoring (p-CGM)-based care as compared with standard care in the management of patients with type 1 and type 2 diabetes.

Materials and methods: The PubMed database was searched comprehensively to identify prospective or retrospective studies evaluating p-CGM as a diagnostic tool for subsequent implementation of lifestyle and/or medication changes and reporting glycated haemoglobin (HbA1c) as an outcome measure.

Results: We found 872 articles, 22 of which were included in the meta-analysis. Overall, the use of p-CGM was associated with greater HbA1c reduction from baseline (−0.28%, 95% confidence interval [CI] −0.36% to −0.21%, $I^2 = 0\%$, $P < 0.00001$) than usual care, irrespective of type of diabetes, length of follow-up, frequency of continuous glucose monitoring (CGM) use and duration of CGM recording. In the few studies describing CGM-derived glucose metrics, p-CGM showed a beneficial effect on change in time in range from baseline (5.59%, 95% CI 0.12 to 11.06, $I^2 = 0\%$, $P = 0.05$) and a neutral effect on change in time below the target range from baseline (−0.11%, 95% CI −1.76% to 1.55%, $I^2 = 33\%$, $P = 0.90$).

Conclusions: In patients with type 1 and type 2 diabetes, p-CGM-driven care is superior to usual care in improving glucose control without increasing hypoglycaemia.

KEYWORDS
continuous glucose monitoring, randomized trial, systematic review, type 1 diabetes, type 2 diabetes

1 | INTRODUCTION

Over the past two decades, continuous monitoring of interstitial glucose (CGM) has revolutionized diabetes care, providing both patients and healthcare professionals (HCPs) with comprehensive glucose data for effective and informed decision making.[1]

Personal CGM, including real-time CGM and intermittently scanned CGM, provides immediate feedback on glucose levels and has been associated with improvements in several clinical outcomes, including glycated haemoglobin (HbA1c), glucose variability, hypoglycaemia prevalence,

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overall well-being, treatment satisfaction, and fear of hypoglycaemia, in both randomized clinical trials (RCTs) and real-world studies, as compared to self-monitored blood glucose (SMBG).[2,3] Indeed, personal CGM is currently recommended by national and international guidelines as the standard for glucose monitoring in both youth and adults with type 1 diabetes.[4,5] However, it requires long-term supply, continuous wear of monitoring devices, and constant patient commitment.[6]

Unlike personal CGM, professional CGM (p-CGM) systems are owned by the clinic and worn by the patients only for short periods of time to enable retrospective CGM data analysis.[7] Three alternative p-CGM systems are currently available on the market, each with slightly different technical characteristics (Table S1).[8,9] Of note, the patient is blinded to sensor glucose readings and does not receive any glucose-related alert or notification while wearing a p-CGM device, therefore, the HCP can view results that have not been influenced by a patient's decisions in real time.[10] The availability of unbiased glucose data is expected to improve the HCP's understanding of the diverse factors possibly affecting the patient's glycaemic control and guide more appropriate therapeutic intervention, including changes in diet, physical activity (PA), and medications.[6] In addition, sharing the p-CGM report pages with the patient may exert a strong educational effect, promote constructive interactions with the diabetes team, and enhance patient motivation and engagement in diabetes self-management.[11]

Professional CGM has been proposed in patients with type 1 diabetes not achieving optimal glycaemic control, when fasting hyperglycaemia is a recurring issue, when hypoglycaemia unawareness is suspected, and for patients with type 2 diabetes who are frail/unstable.[12] Patients who have additional indications from international guidelines include: (a) those who are newly diagnosed with diabetes mellitus; (b) those with problematic hypoglycaemia but no access to personal CGM; (c) those with type 2 diabetes treated with noninsulin therapies (episodic use as an educational tool); or (d) those who would like to learn more about CGM before committing to daily use.[13] However, evidence supporting the efficacy/effectiveness of a p-CGM-based approach in the management of patients with type 1 and type 2 diabetes is still inconclusive.[14-17]

The aim of this meta-analysis was to evaluate the effect on glucose control of p-CGM-based care as compared with standard care in the management of patients with type 1 and type 2 diabetes.

2 | MATERIALS AND METHODS

2.1 | Statistical methods

This meta-analysis was registered on PROSPERO (CRD42022314480) and performed in agreement with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement (Table S1). We performed an extensive search for relevant data sources in the PubMed online database using the following keywords: "professional continuous glucose monitoring", "retrospective continuous glucose monitoring", "masked continuous glucose monitoring", "professional flash glucose monitoring", "professional-mode flash glucose monitoring", "Dexcom G4 PLATINUM Professional", "Dexcom G6 Pro", "iPro2", "Freestyle Libre Pro", "Freestyle LibrePro", "CGMS", "GlucoDay" and "diabetes." No other filters were used. References of included studies were searched for additional articles. The search was last updated on August 17, 2022. Two investigators (S.D.M., I.C.) performed the literature search and article retrieval and selection independently. Any controversy was settled by debate.

Inclusion criteria for article selection were: (a) either prospective or retrospective clinical studies evaluating p-CGM as a diagnostic tool for subsequent implementation of lifestyle and/or medication changes; (b) comparison with standard, non p-CGM-driven care; (c) inclusion of patients with type 1 and type 2 diabetes; (d) reporting absolute change in HbA1c from baseline to the end of intervention as an endpoint of the study or change in HbA1c from baseline to the end of intervention being obtainable from the data reported in the article; (e) articles written in the English language. Studies evaluating pregnant women with diabetes were excluded.

Two investigators (S.D.M., I.C.) performed data extraction independently using a piloted datasheet and collected the following data: (a) general information on the study (eg, authors, year of publication, sample size, type of diabetes); (b) mean change from baseline in HbA1c in patients allocated to p-CGM and non-p-CGM groups who completed the study; (c) number of p-CGM intervention periods; (d) duration of follow-up; (e) duration of CGM; (f) number of studies enrolling patients with type 1 and type 2 diabetes or both; (g) number of observational studies and RCTs. As in previous literature,[18,19] we decided to include both RCTs and observational studies in our meta-analysis due to clinical relevance and the complementary nature of the data provided by either type of study, despite their methodological differences.[20] To account for these differences, a subgroup analysis according to study type was planned.[21]

Whenever possible, missing mean HbA1c differences from baseline were calculated using Review Manager (RevMan), version 5.4, The Cochrane Collaboration, 2020. If standard deviation (SD) was missing, it was calculated from standard error (SE) or 95% confidence interval (CI). When only SE was indicated, we calculated SD by multiplying the SE by the square root of the sample size; when only 95% CI was indicated, we calculated SD by dividing the length of the CI by 3.92, and then multiplying by the square root of the sample size. Otherwise, corresponding authors were contacted to retrieve missing data.

The primary outcome was mean difference of change in HbA1c from baseline between patients receiving p-CGM-driven care for diabetes and patients receiving usual care. The meta-analysis was performed using RevMan, version 5.4, The Cochrane Collaboration, 2020. Data were analysed as continuous variables and summarized as mean differences. Pooled data were presented with 95% CI; heterogeneity between studies was assessed using *I*-squared and values ≥50% were regarded as high. Subgroup analyses based on type of diabetes, number of intervention periods with p-CGM, duration of follow-up and type of study design were performed. For the studies reporting this outcome, the role of p-CGM-driven care in

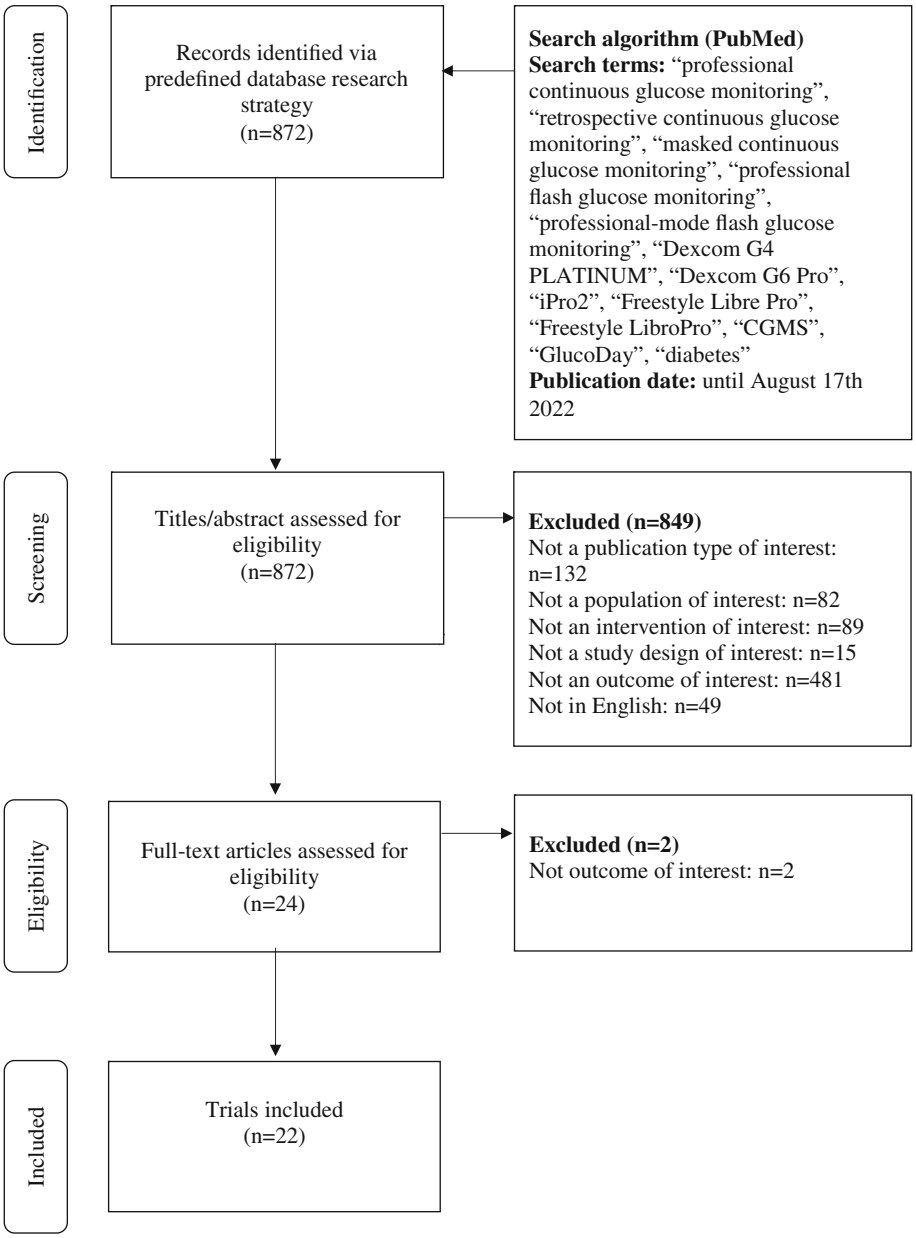

FIGURE 1 PRISMA flowchart for study selection

improving time spent within and below the target range was also evaluated. The risk of bias of included studies was assessed independently by two investigators (S.D.M., I.C.) with the Cochrane Collaboration's tool for RCTs and the National Heart, Lung, and Blood Institute Quality Assessment Tool for observational studies.

3 | RESULTS

We found 872 articles, of which 22 met the inclusion/exclusion criteria and were included in the meta-analysis (Figure 1). Details of the included studies are available in Table S2. Thirteen out of 22 studies were supported financially and/or with materials by companies. All included studies reported outcomes only of patients with type 1 or type 2 diabetes, with the exception of three articles[22-24] which reported outcomes of patients with both types of diabetes. Specifically, one single study, an RCT, described a mixed type 1/type 2 diabetes cohort,[24] while the other two reported outcomes for each type of diabetes as separate cohorts[22,23]; thus, 24 data sources were identified. Thirteen studies were conducted in patients with type 2 diabetes,[11,17,22,23,25-33] seven of which were RCTs, four were observational retrospective studies, one was a nonrandomized prospective study, and one was a quasi-experimental prospective study. Ten studies were conducted in patients with type 1 diabetes,[22,23,34-41] nine of which were RCTs and one was a retrospective study. Six out of these 10 studies included only children and adolescents, two studies only adults, and two other studies both paediatric and adult patients.

Two studies[37,39] had a crossover design: Ludvigsson et al reported mean HbA1c values at baseline and after 12 weeks of intervention, pooling the p-CGM ("blinded") and SMBG ("open") phases,

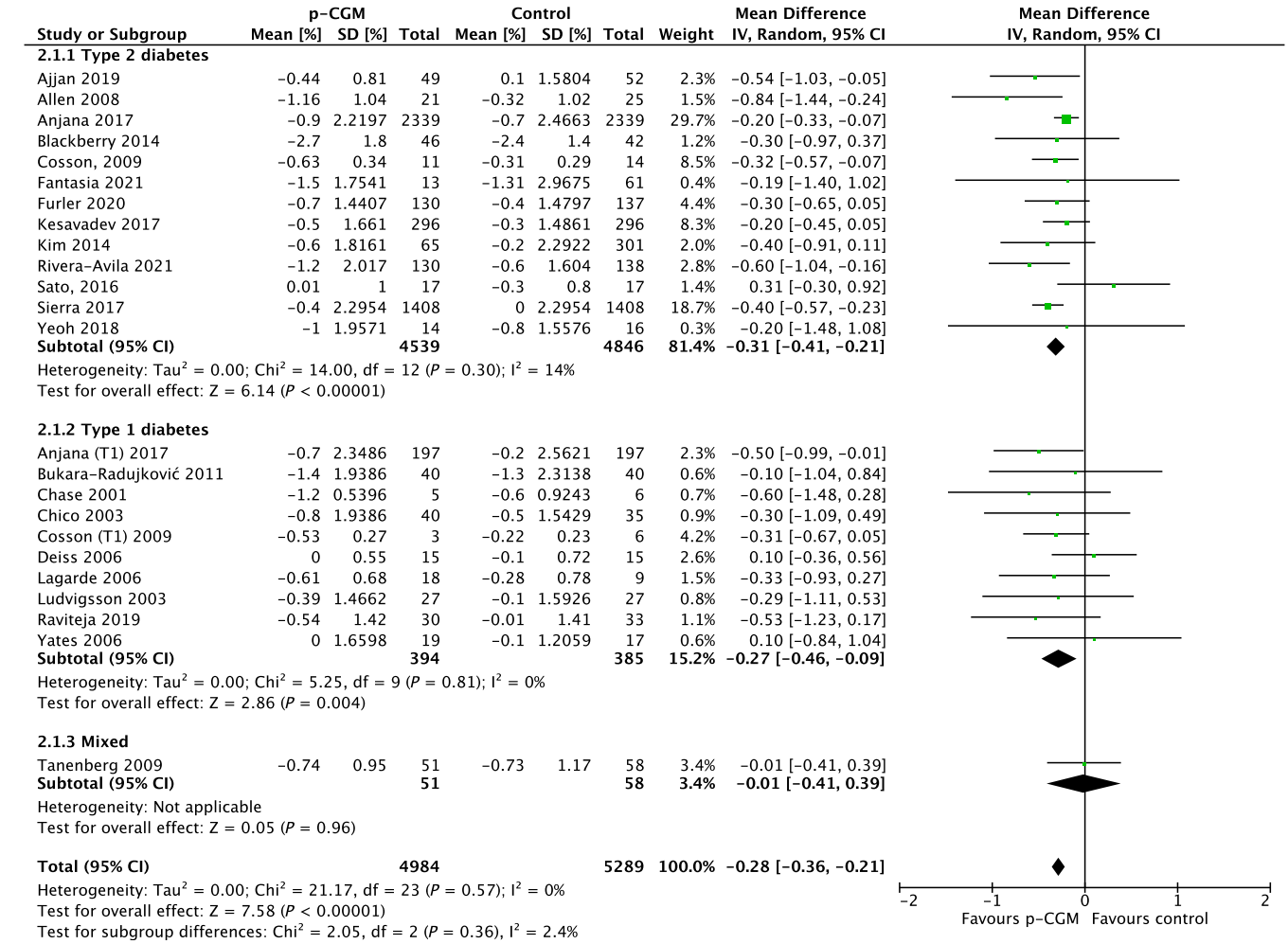

FIGURE 2 Forest plot for the difference in change in glycated haemoglobin from baseline in patients receiving professional continuous glucose monitoring (p-CGM)-driven care versus usual care according to type of diabetes. CI, confidence interval

respectively[39]; in contrast, Deiss et al reported mean HbA1c values at three time points (baseline, mid-way, and after crossover) with no separate calculation per study phase.[37] For the latter study, we used the data related to the first period of intervention.

Overall, use of p-CGM was associated with greater reduction in HbA1c from baseline compared with usual care (−0.28%, 95% CI −0.36% to −0.21%, $I^2 = 0\%$, $P < 0.00001$). Importantly, the benefit was observed both in patients with type 2 (−0.31%, 95% CI −0.41% to −0.21%, $I^2 = 14\%$, $P < 0.00001$) and type 1 (−0.27%, 95% CI −0.46% to −0.09%, $I^2 = 0\%$, $P = 0.004$) diabetes (Figure 2). The single study reporting data from a mixed population of type 1 and type 2 diabetes[24] produced neutral results (−0.01%, 95% CI −0.41% to 0.39%, $I^2 = 0\%$, $P = 0.96$), but it was limited by a small sample size. Nonetheless, no relevant heterogeneity was detected between the three subgroups ($I^2 = 2.4\%$).

Superiority of p-CGM was ascertained both in studies with a relatively short follow-up duration, specifically ≤3 months (−0.26%, 95% CI −0.36% to −0.17%, $I^2 = 0\%$, $P < 0.00001$), and in studies with a longer follow-up, namely, >3 but ≤6 months (−0.23%, 95% CI −0.43% to −0.04%, $I^2 = 0\%$, $P = 0.02$), and >6 months (−0.31%, 95% CI −0.55% to −0.07%, $I^2 = 45\%$, $P = 0.01$ [Figure 3]). No heterogeneity between subgroups was detected ($I^2 = 0\%$) and the only study with a duration >6 months displaying a trend toward benefit in favour of SMBG had an exiguous sample size.[31]

Both one and more than one period of intervention with p-CGM were associated with a remarkable effect on HbA1c (−0.30%, 95% CI −0.38% to −0.22%, $I^2 = 0\%$, $P < 0.00001$; −0.21%, 95% CI −0.40% to −0.03%, $I^2 = 0\%$, $P = 0.02$), with no heterogeneity between subgroups ($I^2 = 0\%$ [Figure S1]).

Moreover, p-CGM was found to be beneficial regardless of CGM duration (≤3 days: −0.27%, 95% CI −0.41% to -0.13%, $I^2 = 0\%$, $P = 0.0002$; >3 days: −0.30%, 95% CI −0.39% to -0.20%, $I^2 = 0\%$, $P < 0.00001$ [Figure S2]) and study design (RCTs: −0.26%, 95% CI −0.39% to −0.14%, $I^2 = 0\%$, $P < 0.00001$; observational studies: −0.30%, 95% CI −0.41% to −0.20%, $I^2 = 0\%$, $P < 0.00001$ [Figure S3]).

Five studies,[17,22,25,27,31] all including patients with type 2 diabetes, also reported the time spent within and outside the target glucose range (3.9–10 mmol/L in three studies, 3.9–8.3 mmol/L in one other study, and 3.9–7.8 mmol/L in the remaining study), as recorded by

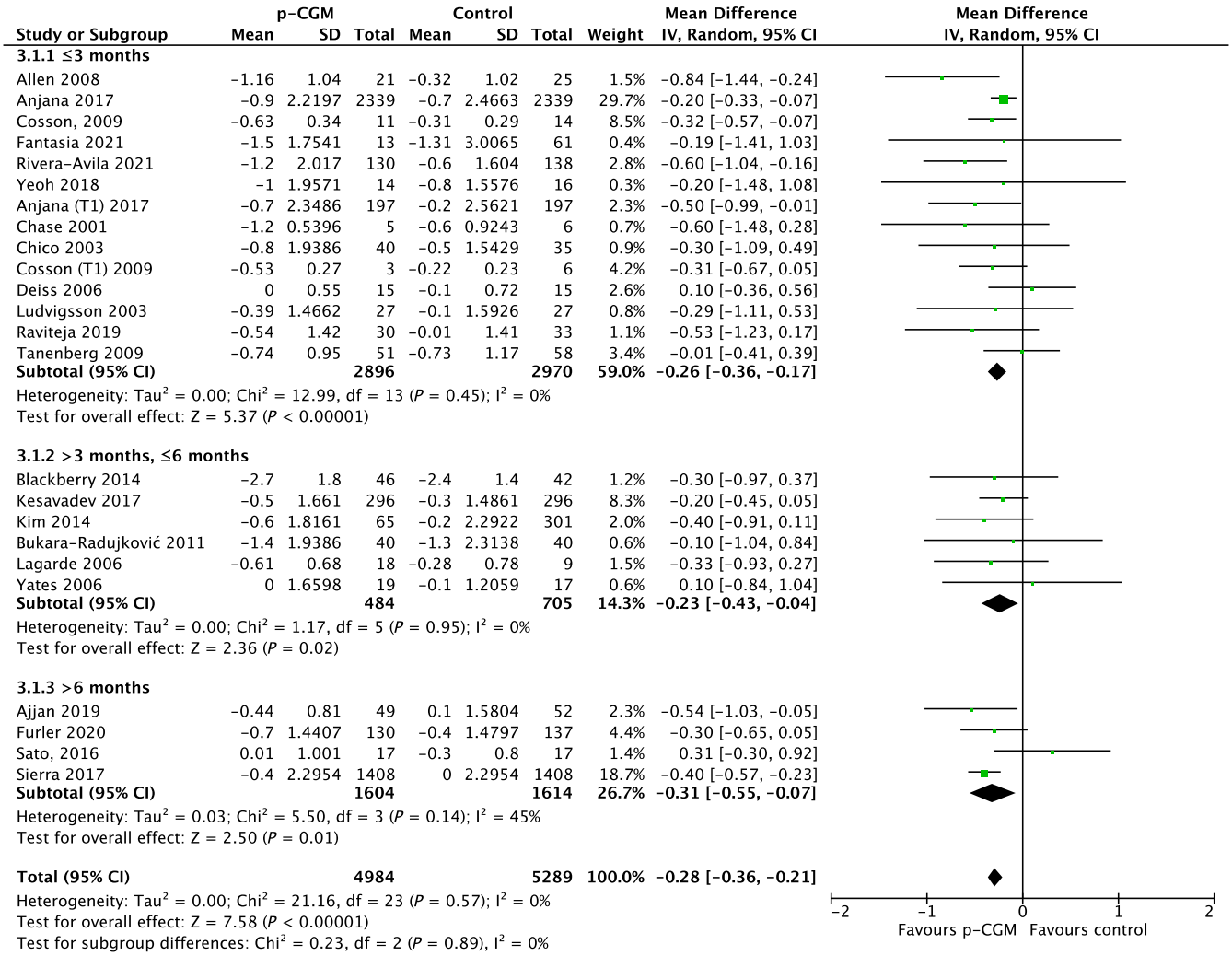

FIGURE 3 Forest plot for the difference in change in glycated haemoglobin from baseline in patients receiving professional continuous glucose monitoring (p-CGM)-driven care versus usual care according to length of follow-up. CI, confidence interval

p-CGM in both the intervention (p-CGM-driven care) and control group (CGM data not disclosed to the physician and the patient). When pooling together the three studies[17,25,27] reporting the time spent in the 3.9 to 10 mmol/L glucose range and the four studies[22,25,27,31] reporting the time spent below 3.9 mmol/L, p-CGM-driven care was associated with a greater increase in time in range (5.59%, 95% CI 0.12 − 11.06, $P = 0.05$ [Figure 4]) and a nonsignificant reduction of time below range (−0.11%, 95% CI −1.76% to 1.55%, $I^2 = 33\%$, $P = 0.90$ [Figure 5]) compared with standard care, respectively.

The risk of bias of included studies was assessed independently by two investigators (S.D.M., I.C.) with the Cochrane Collaboration's tool for RCTs (Figures S4, S5) and the National Heart, Lung, and Blood Institute Quality Assessment Tool for observational studies. The quality of included observational studies (n = 5) was rated as fair, with risk of biases mostly concerning lack of sample size calculation, lack of blinding and, in two studies,[28,29] lack of adjustment for potential confounding factors. A sensitivity analysis including only RCTs with a reasonably low risk of bias was performed, confirming the favourable effect of p-CGM on HbA1c change (−0.29%, 95% CI −0.42 to −0.16, $P < 0.00001$ [Figure S6]).

4 | DISCUSSION

The results of this meta-analysis reveal that p-CGM-driven care for diabetes, where p-CGM is applied as a diagnostic tool for glucose pattern recognition and subsequent implementation of lifestyle and/or medication changes, is superior to usual care in improving glucose control across a wide range of age groups, irrespective of type of diabetes, length of follow-up, frequency of CGM use, and duration of CGM recording.

Overall, use of p-CGM resulted in a reduction of HbA1c from baseline by 0.28% compared with usual care. This is very close to 0.3%, which is generally considered a clinically meaningful reduction to reduce diabetic complications in the long term[42-44] and was also recommended as a noninferiority margin by the Food and Drug Administration.[45,46] Furthermore, our findings are in line with the

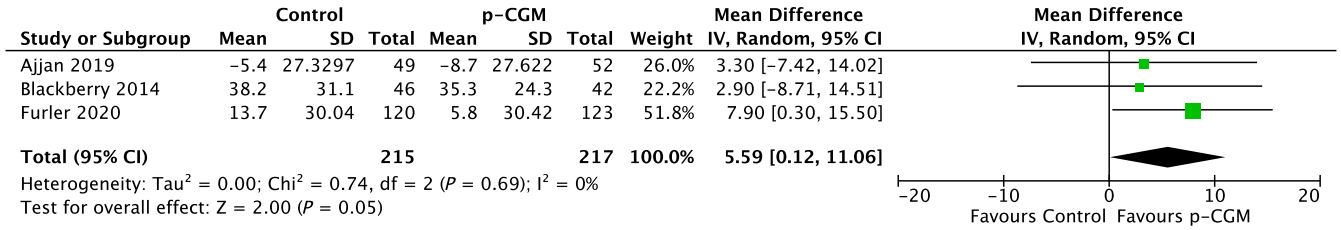

FIGURE 4 Forest plot for the difference in change in time in range from baseline in patients receiving professional continuous glucose monitoring (p-CGM)-driven care versus usual care. CI, confidence interval

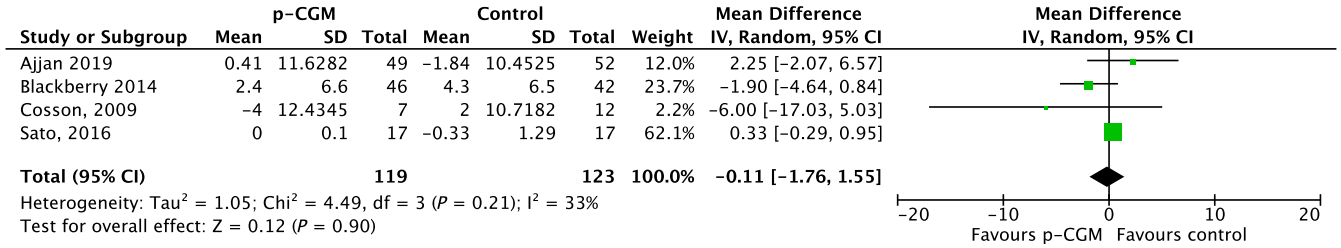

FIGURE 5 Forest plot for the difference in change in time below range from baseline in patients receiving professional continuous glucose monitoring (p-CGM)-driven care versus usual care. CI, confidence interval

results of recent meta-analyses evaluating real-time CGM (−0.24%) or real-time CGM and intermittently scanned CGM as a whole (−0.17%).[47,48] Earlier meta-analyses showed that p-CGM does not differ from control in reducing HbA1c levels in patients with type 1 diabetes[14] and type 2 diabetes.[15] However, our analysis included more data sources (10 for type 1 diabetes, 13 for type 2 diabetes, and 1 for mixed type 1/type 2 diabetes patients) and compared outcomes obtained with four different devices, including newer-generation devices. Moreover, it should be noted that the meta-analysis by Ida et al included two studies[49,50] evaluating the unmasked Freestyle Libre (Abbott Diabetes Care, Inc., Alameda, California) device. In these two studies, adjustments of insulin doses were made by the investigators based on retrospectively reviewed glucose profiles; however, an effect of patients' real-time access to their own glucose readings on HbA1c levels at the end of the intervention phase cannot be ruled out. In contrast with Ida et al, only studies evaluating purely professional devices, with the participants being blinded to their glucose readings for the whole sensor lifetime, were included in this meta-analysis.

In recent years, along with the spread of CGM as a diagnostic and therapeutic tool for diabetes management, several new metrics of glucose control and variability have emerged, with the time spent in the 3.9 to 10 mmol/L glucose range being considered useful both as a clinical target and an outcome measure complementing HbA1c for the majority of patients with type 1 and type 2 diabetes.[13,51] Of note, as a change in time in range 3.9 to 10 mmol/L of 10% is associated with a change in HbA1c of 0.5% to 0.8% in the opposite direction,[13] each incremental 5% increase in the former should be regarded as clinically significant for improving glucose control. In our analysis, consistent with the greater effect on HbA1c, use of p-CGM resulted in more favourable changes in time in range 3.9 to 10 mmol/L than usual care in all the three studies reporting this outcome, with a mean difference of 5.56% between the two groups.

Four out of 22 included studies also evaluated change in time spent below 3.9 mmol/L as a nonprimary endpoint. Overall, use of p-CGM was associated with a small nonsignificant reduction of time spent with < 3.9 mmol/L compared to standard care. In contrast to our results, in a pooled analysis of three studies conducted in patients with type 2 diabetes, Ida et al found that time spent with < 3.9 mmol/L was significantly reduced in the p-CGM group as compared with the SMBG group.[15] Again, two of these three studies actually evaluated the Freestyle Libre device,[49,50] providing availability of unmasked glucose readings and allowing any subsequent patient intervention for hypoglycaemia avoidance/treatment: this may have contributed to the reduction of time below range in the CGM group. Specifically, in the REPLACE study, time spent with < 3.9 mmol/L was reduced by 43% (−0.47 ± 0.13 h/d; mean ± SE) in the intervention compared with control ($P = 0.0006$) group,[50] thus driving the result of the pooled analysis.

This meta-analysis has some limitations that need to be addressed. First, we only selected articles written in English. Second, only a minority of the included studies reported the innovative CGM-derived glucose metrics for both the intervention and control groups, so further research is needed to clarify the effects of p-CGM on these outcomes. Third, even if in our analysis the superiority of p-CGM has been ascertained for any length of follow-up, we acknowledge that studies with duration longer than 6 months are limited in number, and therefore this finding should be regarded with caution. Fourth, non-glycaemic outcomes (eg, change in body weight, blood pressure, treatment satisfaction, diabetes distress) were not evaluated. Of note, discussing the reports of p-CGM with HCPs may potentially increase patient awareness of the effects of diet and exercise on blood glucose

levels, and in turn promote positive lifestyle changes and increase PA,[11,26] with possible benefits with regard to cardiovascular risk factors. Fifth, as most of the cohorts of patients with type 2 diabetes were treated with insulin and/or noninsulin-based drugs and no separate outcomes were given according to type of therapy, evidence in noninsulin-treated patients is still inconclusive. In their 8-week randomized trial, Allen et al demonstrated that, in individuals with type 2 diabetes not treated with insulin, PA counselling and review of drug therapy using 3-day p-CGM feedback may improve PA levels and reduce HbA1c as compared with usual care.[26] In contrast to this finding, a retrospective 6-month evaluation of 296 adults (91% on some form of insulin treatment with oral antidiabetic drugs, 7% on one or more oral antidiabetic drugs without insulin, 2% on glucagon-like peptide-1 receptor agonists) undergoing a 6- to 7-day study of their glycaemic profile with p-CGM found a significantly greater reduction of HbA1c than the control group only in patients treated with basal-bolus insulin, biphasic insulin, or continuous subcutaneous insulin infusion therapy.[29]

Self-monitored blood glucose is a cornerstone of diabetes care and has been associated with HbA1c reductions in both type 1 and type 2 diabetes.[52-55] Indeed, appropriate use of SMBG data can facilitate patient understanding and self-management and support HCPs in providing individualized recommendations on lifestyle and medications.[56] In our vision, the incremental value of p-CGM is attributable both to the greater number of readings facilitating the identification of diurnal and nocturnal patterns of glucose variation and to the availability of easy-to-read graphs and charts stimulating a sounder discussion between the patients and HCP. We also believe the p-CGM-associated benefit may add to that of other ongoing therapeutic approaches.

In the last decade, the marketing of ever smaller and more accurate personal CGM devices, with easy sharing of glucose data and possible integration with insulin delivery devices, has revolutionized daily diabetes self-management. Despite their unquestionable benefits for glucose control, hypoglycaemia and quality of life, the use of such devices still involves fewer than 50% of patients with type 1 diabetes in the United States and Western Europe, and fewer than 25% of patients in the rest of the world.[57,58] CGM use in type 2 diabetes is much more marginal, accounting for fewer than 2% of patients according to a digital self-report survey of diabetes practices conducted in Italy in 2019.[59] Commonly reported barriers to commencement and continuation of personal CGM include cost of device and supplies, restrictive coverage eligibility criteria, not wanting a diabetes device on the body, painful insertions, skin irritations/adhesive problems, nuisance of alarms, interference with sleep, not understanding what to do with the information, or specific features of the device.[60] Intermittent p-CGM may overcome some of these barriers, providing the HCPs with more comprehensive glucose data, recorded under routine living conditions, for possible medication and/or lifestyle adjustments, at the same time limiting the inconvenience of constantly wearing a device and saving the costs of long-term supplies. For instance, when a patient is not reaching his/her HbA1c target, the placement of a sensor 1 to 2 weeks before a scheduled visit at the diabetes clinic would make glucose data available for evaluation and discussion at the time of the visit.[10] The results of our meta-analysis suggest that this approach is effective at improving glucose control without increasing hypoglycaemia in patients with both type 1 and type 2 diabetes.

In conclusion, p-CGM involves patients wearing for a short period of time (up to 2 weeks) a CGM device provided by their diabetes clinic, with subsequent device download and analysis of glucose data for possible adjustment of diabetes medications and/or lifestyle. This systematic review and meta-analysis of prospective and retrospective clinical studies evaluating p-CGM as a diagnostic tool for clinicians in patients with type 1 and type 2 diabetes shows that p-CGM-driven care is superior to usual care in improving glucose control without increasing hypoglycaemia.

AUTHOR CONTRIBUTIONS

Sergio Di Molfetta: conceptualization, methodology, writing – original draft; Irene Caruso: formal analysis, writing – original draft; Angelo Cignarelli, Annalisa Natalicchio, Luigi Laviola, Sebastio Perrini: writing – review and editing; Francesco Giorgino: supervision, writing – review and editing.

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CONFLICT OF INTEREST

Sergio Di Molfetta has received speaker fees from Ascensia Diabetes Care and Roche Diabetes Care Italy and has provided advisory services to Alpha-Pharma Service Srl, Ascensia Diabetes Care, Eli-Lilly and Roche Diabetes Care Italy. Irene Caruso has received speaker fees from Eli Lilly and Novo Nordisk. Angelo Cignarelli has received speaker fees from Sanofi, Recordati, Eli Lilly, Novo Nordisk, Mundipharma and Boehringer-Ingelheim. Annalisa Natalicchio has received speaker fees from AstraZeneca, Novo Nordisk and Sanofi. Sebastio Perrini declares no relevant conflict of interest. Luigi Laviola has

received consultant fees and speaker fees from Abbott, AstraZeneca, Boehringer-Ingelheim, Eli Lilly, MOVI, Medtronic, Menarini, NovoNordisk, Roche Diabetes Care, Sanofi and Terumo. Francesco Giorgino has served as an advisor for AstraZeneca, Boehringer Ingelheim, Eli Lilly, Merck Sharp & Dohme, Medtronic, Novo Nordisk, Roche Diabetes Care and Sanofi, and as a research investigator for Eli Lilly, Novo Nordisk and Roche Diabetes Care, and has received grants from Eli Lilly and Roche Diabetes Care.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/dom.14981.

DATA AVAILABILITY STATEMENT

The datasets generated during and/or analyzed in the current study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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